



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,516	04/03/2002	Michel G. Bergeron	GGD-31611-PCTUS	5405
22202	7590	11/04/2005	EXAMINER	
WHYTE HIRSCHBOECK DUDEK S C			HUYNH, PHUONG N	
555 EAST WELLS STREET			ART UNIT	
SUITE 1900			PAPER NUMBER	
MILWAUKEE, WI 53202			1644	

DATE MAILED: 11/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/980,516

Applicant(s)

BERGERON ET AL.

Examiner

Phuong Huynh

Art Unit

1644

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 September 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 and 24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-20 and 24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date: _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/19/05 has been entered.
2. Claims 1-20 and 24 are pending and are being acted upon in this Office Action.
3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
4. Claims 1-10 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a formulation which comprises an antibody or antigen binding fragment thereof that binds specifically to HLA-DR being coupled to a lipid-comprising vesicle wherein the antibody or binding fragment thereof is capable of binding to a HLA-DR protein present at the surface of an infectious agent or at the membrane surface of a cell, (2) the said formulation wherein the vesicle is a liposome, (3) the said formulation wherein the liposome is a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10: 1 and 1: 1, wherein the acyl chains are either saturated or unsaturated and have been between 14 and 18 carbon atoms in length, (4) the said formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine, (5) the said formulation wherein the liposome comprises polyethyleneglycol that has a molecular weight between 500 and 5000 daltons, (6) the said formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio is 10: 3, (7) the said formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine: diacylphosphatidylglycerol: diacylphosphatidylethanolamine polyethyleneglycol in a molar ratio of 10:3:0.1-3, (8) the said formulation wherein the liposome comprises a mixture of dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol in a molar ratio of 10:3 or distearoylphosphatidylcholine: distearoylphosphatidylglycerol in

Art Unit: 1644

a molar ratio of 10:3, (9) the said formulation wherein the liposome comprises a mixture of dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol: dipalmitoylphosphatidylethanolamine-polyethyleneglycerol in a molar ratio of 10:3:0.33 or dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol in a molar ratio of 10:3:0.83 and (10) the said formulation which comprises a drug wherein the drug is selected from the group consisting of AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin, **does not** reasonably provide enablement for (1) any formulation which comprises any ligand capable of binding to a HLA-DR protein present at the surface of any infectious agent and the membrane of any cell as set forth in claims 1-9, (2) said formulation further comprising any additional ligand to any one or more proteins such as the ones recited in claims 10 and claims 17-18, (3) said formulation further comprising any additional drug such as the ones recited in claims 19-20. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification defines the term "ligand" as any surface antigen, any agonist, any antagonist and any antibody molecule such as whole and antibody fragment capable of binding to any protein of interest (see paragraph bridging pages 5 and 6). The claims encompasses any formulation which comprises any ligand such as any antigen, any agonist, any antagonist and any antibody capable of binding to any HLA-DR present at the surface of any infectious agent and at the membrane surface of any cell wherein the ligand being coupled to any lipid-comprising vesicle. However, the specification discloses only anti-HLA-DR immunoliposome comprising antibody or binding fragment thereof that binds specifically to HLA-DR coupled to liposomes such as the ones discloses on page 7. The only infectious agent that expressed HLA-DR is HIV virus.

The specification does not teach how to make any ligand coupled to any lipid comprising vesicle mentioned above because there is insufficient guidance as to the structure of the ligand such as any antigen, any agonist, any antagonist that binds to any HLA-DR protein without the chemical structure and/or amino acid sequence. Further, there is insufficient guidance as to which other infectious agent that HLA-DR protein is present on the surface other than HIV. Given the unlimited number of formulation comprising any ligand that encompassed any agonist, antagonist and/or any antigen that binds HLA-DR coupled to any lipid comprising vesicle, there is insufficient number of in vivo working example demonstrating the claimed undisclosed ligand is effective in targeting any lipid vesicle or liposomes to any and all infectious agent and any and all cells for treating any number of diseases.

Phillips et al (PTO 1449) teach liposome such as lipophilic poly(ethylene glycol) derivatives coupled to a ligand such as CD4+ antibody or F(ab)2 enhances the immunogenicity does not offer any advantage in terms of targeting efficiency to PBMCs, and appears to be disadvantageous with respect to enhance immunogenicity of the conjugate (see abstract, page 3173, col. 2, in particular). Phillips et al further teach repeated administration of anti-CD4 (Fab)2 fragment coupled to immunoliposomes induced significant levels of anti-CD4+ (GK1.5) after only one i.v. injection (see abstract, page 3172, col. 2, first paragraph, in particular). Phillips et al conclude that this therapeutic approach may be limited unless the immunogenicity of the targeting antibody can be drastically reduced or inhibited (see page 3172, col. 2, first paragraph, in particular). The targeting efficacy in vivo is significantly reduced due to metabolic clearance as a consequence of repeated immunoliposome injection (see page 3173, col. 1, in particular).

As such, the formulation, mode of delivery means, and types of ligand being coupled to the type of lipid-comprising vesicle is not predictive of the targeting lipid-containing vesicle or liposome to all infectious agent and all cell types in vivo as a method of treating any and all infectious diseases.

In view of the lack of guidance as to the structure of the ligand such as agonist, antagonist and antigen that binds to HLA-DR being coupled to any type of liposome, and the lack of vivo working example, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

5. Claims 1-10 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any formulation which comprises any ligand capable of binding to a HLA-DR protein present at the surface of any infectious agent and the membrane of any cell as set forth in claims 1-9, (2) said formulation further comprising any additional ligand to any one or more proteins such as the ones recited in claims 10 and claims 17-18, (3) said formulation further comprising any additional drug such as the ones recited in claims 19-20.

The specification defines "ligand" as any surface antigen, any agonist, any antagonist and any antibody molecule such as whole and antibody fragment capable of binding to any protein of interest (see paragraph bridging pages 5 and 6). The claims encompasses any formulation which comprises any ligand such as any antigen, any agonist, any antagonist and any antibody capable of binding to any HLA-DR present at the surface of any infectious agent and at the membrane surface of any cell wherein the ligand being coupled to any lipid-comprising vesicle. However, the specification discloses only anti-HLA-DR immunoliposome comprising antibody or binding fragment thereof that binds specifically to HLA-DR coupled to liposomes such as the ones discloses on page 7. The only one infectious agent that expressed HLA-DR is HIV virus.

With the exception of the specific formulation comprising the specific anti-HLA-DR being coupled to the specific liposome wherein the anti-HLA antibody is capable of binding to HLA protein present at the surface of HIV or at the membrane surface of host cells such as CD4+ T lymphocytes, monocytes and macrophages, there is insufficient written description about the structure associated with function of any ligand that encompasses any antigen, any agonist and any antagonist that binds to HLA-DR protein in the claimed formulation. This is because a ligand, agonist and/or antagonist that binds to any HLA-DR protein have no structure without the chemical structure and/or amino acid sequence has no structure, much less function. Further,

Art Unit: 1644

there is insufficient written description about the lipid-comprising vesicle being coupled to undisclosed ligand mentioned above. The only infectious agent that expressed HLA-DR is HIV virus. The rest of the infectious agent that expressed the HLA-DR protein are not adequately described. Since the structure of the ligand and the structure of the lipid-comprising vesicle or liposome in the claimed formulation is not adequately described, it follows that any formulation comprising any undisclosed ligand coupled to any undisclosed lipid-comprising vesicle mentioned above further comprises any additional ligand or any additional drug are not adequately described.

The specification discloses only anti-HLA-DR antibody being coupled to the specific liposome as set forth on page 7, lines 5-25, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of ligand that binds to HLA-DR coupled to the a representative number species of lipid containing vesicle or liposomes to describe the genus for the claimed formulation. Thus, Applicant was not in possession of the claimed genus. See *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-2, 10-20 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0286418 A1 (December 10, 1988; PTO 1449) as evidence by Saarloos et al (J Virology 71(3): 1640-1643, Feb 1997; PTO 1449).

The '418 patent teaches a formulation which comprises a ligand such as antibodies or antibody fragments capable of binding to class II antigens (which is another name for HLA-DR) present at the surface of an infectious agent such as HIV virus and the membrane of a host cell such as monocytes or CD4 positive lymphocytes wherein the reference ligand being coupled to a lipid comprising vesicle such as liposome (see page 15, lines 35-38, page 15, lines 20-30, in

Art Unit: 1644

particular). The reference class II antigens inherently are HLA-DR protein as evidence by the Saaroloos et al (see page 1640, col. 1, second paragraph, in particular). The reference formulation further comprises an additional ligand that binds to CD4 (see page 15, lines 37, in particular). The reference formulation further comprises a drug such as ddCTP, azidothymidine triphosphate (AZT), (see page 15, line 35, claims 3-8, in particular). Thus, the reference teachings anticipate the claimed invention.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).
10. Claims 1-2, 10-18 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selvam et al (of record, Antiviral Research 33: 11-20, 1996; PTO 892) or Desormeaux et al (J Drug Targeting 6(1): 1-15, 1998; PTO 1449) each in view of Saaroloos et al (J Virology 71(3): 1640-1643, Feb 1997; PTO 1449) and Catin et al (of record, J Virology 71(3): 1922-1930, March 1997; PTO 892).

Selvam et al teach a formulation which comprises a ligand such as anti-CD4 (whole) capable of binding to CD4 expressed on infectious agent such as HIV virus and CD4+ T cells wherein the reference ligand is coupled to a lipid-comprising vesicle such as liposome (See abstract, page 15, col. 1, in particular). The reference formulation comprises a drug such as 20-mer antisense DNA sequence of the rev HIV-1 regulatory gene in the form of phosphorothioate oligonucleotide against infectious agent such as HIV (see abstract, in particular). Selvam et al

teach tagging liposome with anti-CD4 monoclonal antibody would allow the liposomes to be targeted to a specific cell population since HIV predominantly attacks cells that bear CD4 receptor (see page 12, col. 1, last paragraph, in particular).

Desormeaux et al teach a formulation which comprises a ligand such as antibodies capable of binding to CD4 expressed on infectious agent such as HIV virus and CD4+ T cells wherein the reference ligand is coupled to a lipid-comprising vesicle such as liposome (See entire document, abstract, page 3, col. 1, in particular). The reference formulation further comprises an anti-viral drug such as ZAT, ddC, foscanet, ddITP, (see page 3, col. 1, Drug containing liposomes against HIV infection, in particular). Desormeaux et al teach site-specific drug targeting may allow less frequent administrations of anti-viral agents and at low doses (reduced toxicity) than convention therapy that improves efficacy, and quality of life for patients (see page 11, Advantages and Limitations, Table 1, in particular).

The claimed invention in claim 1 differs from the teachings of the references only in that the formulation wherein the ligand is capable of binding to a HLA-DR protein instead of CD4.

The claimed invention in claims 17 and 19 differs from the teachings of the references only in that the formulation wherein the ligand is capable of binding to a HLA-DR protein and further comprises an additional ligand to CD4.

Saarloos et al et al teach a ligand such as anti-HLA-DR (class II MHC) that binds to HLA protein present at the surface of an infectious agent such as HIV and at the membrane surface of a cell such as CD4+ T cells and macrophage (see entire document, page 1641, col. 2, page 1642, col. 1, in particular).

Catin et al teach infectious agent such as HIV acquired host protein such as HLA-DR, ICAM-1 (CD54), CD55 (DAF), CD59, CD63 and CD71 (see page 1922, col. 1, in particular). Catin et al teach antibody to HLA-DR or anti-LFA-1 (CD11a) inhibit HIV infection since HIV virus acquired host cellular protein on the surface of the progeny virus (see page 1922, col. 1, in particular). Catin et al teach CD4 molecule is the primary cell surface receptor for HIV-1 (page 1922, col. 2, in particular). Catin et al teach HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 (see page 1922, col. 2, in particular). The reference HLA-DR protein is expressed in lymphoid cells such as CD4+ T lymphocytes, and monocyte derived macrophages (see page 1922, col. 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to either substitute the anti-CD4 ligand or combine the anti-CD4 ligand

capable of binding to CD4 protein in the anti-CD4 ligand that coupled to liposome as taught by Selvam et al or Desormeaux et al for the anti-HLA-DR ligand that binds to the surface of HIV and at the membrane surface of T cells as taught by Saarloos et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 as taught by Catin et al (see page 1922, col. 2, in particular) that enhances the kinetics of virus infection (see abstract, in particular). Selvam et al teach tagging liposome with antibody to host-derived molecules acquired by HIV would allow the liposomes to be targeted to a specific cell population since HIV predominantly attacks cells that bear CD4 receptor (see page 12, col. 1, last paragraph, in particular). Saarloos et al et al teach a ligand such as anti-HLA-DR (class II MHC) that binds to HLA protein present at the surface of an infectious agent such as HIV and at the membrane surface of a cell such as CD4+ T cells and macrophage (see entire document, page 1641, col. 2, page 1642, col. 1, in particular). Desormeaux et al teach site-specific drug targeting may allow less frequent administrations of anti-viral agents and at low doses (reduced toxicity) than convention therapy that improves efficacy, and quality of life for patients (see page 11, Advantages and Limitations, Table 1, in particular).

Applicants' arguments filed 9/19/05 have been fully considered but are not found persuasive.

Applicants' position is that Selvam teaches immunoliposomes conjugated to CD4 monoclonal antibody containing a Rev antisense. Selvam does not teach or suggest using any other ligands such as the ligand able to bind to HLA-DR. The populations of cells having HLA-DR at their surface are not necessarily the same population as those having CD4 at their surface. A cell may be CD4 negative and HLA-DR positive and vice versa. Catin et al discuss ways to increase HIV infection using HLA-DR, which in fact points away from inhibiting an infectious agent. There is no teaching or suggestion in either reference, taken alone or in combination, of formulation comprising a ligand capable of binding to protein present at the surface of an infectious agent and at the membrane surface of a cell. The invention does not simply solve the problem of targeting infected cells but also HLA-DR positive non-infected cells and infectious agents carrying HLA-DR themselves. There is no teaching, guidance or direction in Selvam and/or Catin either taken alone or in combination, of methods that may be used in the

identification of a formulation which is capable of binding to a HLA-DR protein present at the surface of an infectious agent and at the membrane surface of a cell.

In response to applicants' argument that Selvam does not teach or suggest using any other ligands such as the ligand able to bind to HLA-DR, the rejection would have been rejected under 102(b) had Selvam teach anti-HLA-DR coupled to liposome. Selvam teaches immunoliposomes conjugated to CD4 monoclonal antibody containing a Rev antisense. However, Saarloos et al teach a ligand such as anti-HLA-DR (class II MHC) that binds to HLA protein present at the surface of an infectious agent such as HIV and at the membrane surface of a cell such as CD4+ T cells and macrophage (see entire document, page 1641, col. 2, page 1642, col. 1, in particular). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to either substitute the anti-CD4 ligand capable of binding to CD4 protein in the anti-CD4 ligand coupled liposome as taught by Selvam et al or Desormeaux et al for the anti-HLA-DR ligand that binds to the surface of HIV and at the membrane surface of a T cells as taught by Saarloos et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

In response to applicants' argument that population of cells having HLA-DR at their surface are not necessarily the same population as those having CD4 at their surface, it is noted that claim 1 merely recites a cell, not a particular population of cell. As long as cells expressing HLA-DR or any infectious expressing HLA-DR, the anti-HLA-DR antibody taught by Saarloos et al being coupled to any liposome as taught by Selvam or Desormeaux et al would have targeted the liposome to said cell or said infectious agent such as HIV expressing HLA-DR.

11. Claims 3-9 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selvam et al (of record, Antiviral Research 33: 11-20, 1996; PTO 892) or Desormeaux et al (J Drug Targeting 6(1): 1-15, 1998; PTO 1449) each in view of Saarloos et al (J Virology 71(3): 1640-1643, Feb 1997; PTO 1449) and Catin et al (of record, J Virology 71(3): 1922-1930, March 1997; PTO 892) as applied to claims 1-2, 10-18 and 24 and further in view of US Pat No 5,773,027 (of record, June 30, 1998; PTO 892).

The combined teachings of Selvam et al, Desormeaux et al, Saarloos et al and Catin et al have been discussed supra.

The invention in claim 3 differs from the teachings of the references only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10: 1 and 1:1 wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length.

The invention in claim 4 differs from the teachings of the references only in that the formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine.

The invention in claim 5 differs from the teachings of the references only in that the formulation wherein the liposome wherein the polyethyleneglycol has a molecular weight between 500 and 5000 daltons.

The invention in claim 6 differs from the teachings of the references only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio is 10: 3.

The invention in claim 7 differs from the teachings of the references only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine: diacylphosphatidylglycerol: diacylphosphatidylethanolamine polyethyleneglycol in a molar ratio of 10:3:0.1-3.

The invention in claim 8 differs from the teachings of the references only in that the formulation wherein the liposome comprises a mixture of dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol in a molar ratio of 10:3 or distearoylphosphatidylcholine: distearoylphosphatidylglycerol in a molar ratio of 10:3.

The invention in claim 9 differs from the teachings of the references only in that the formulation wherein the liposome comprises a mixture of dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol: dipalmitoylphosphatidylethanolamine-polyethyleneglycol in a molar ratio of 10:3:0.33 or dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol in a molar ratio of 10:3:0.83.

The invention in claim 19 differs from the teachings of the references only in that the formulation which comprises a drug wherein the drug is selected from the group consisting of AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin.

The '027 patent teaches a formulation for treatment of viral disease such as HIV which comprises a lipid vesicle or liposome that comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10:1 and 1:1, wherein the acyl

chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length (palmitoyl which is 16 carbon or stearoyl which is 18 carbon in length) (See claim 1 of '027 patent, col. 3, lines 58-62, in particular). The reference formulation wherein the lipid component comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine (see claim 2 of '027 patent, in particular). The reference formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine and wherein the polyethyleneglycol has a molecular weight between about 500 and 5000 Daltons (See claim 11 of '027 patent, in particular). The '027 patent also teaches a formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine (DPPC) and diacylphosphatidylglycerol (DSPG) in a molar ratio of 10:3 (See col. 3, lines 46-47, in particular) and a formulation wherein the lipid component comprises a mixture of diacylphosphatidylcholine: diacylphosphatidylglycerol: diacylphosphatidylethanol-amine-polyethyleneglycol in a molar ratio of 10 to 3 to 1.45 which is between the claimed 0.1-3 (See col. 5, lines 46-47, in particular). The reference formulation further encapsulated a drug such as AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for treating viral infection (See claims 7, 9-10 of '027 patent, in particular). The '027 patent further teaches that the reference liposome formulation can be modified by coupling of antibody molecules to enhance the targeting of the liposome to the specific cells (See col. 4, lines 11-13, in particular) that are HIV reservoirs as well as marked improvement of the pharmacokinetics of drugs (See abstract, in particular). The '027 patent teaches that targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases (See col. 2, lines 25-31, col. 9, lines 7-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the liposome that coupled to anti-HLA-DR capable of binding to a HLA-DR protein as taught by Selvam et al, Desormeaux et al, Saarloos et al and Catin et al for the specific liposome and/or containing drug such as AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for targeting said liposome containing drug to infectious agent such as HIV or cells such as CD4+ T cells or macrophage expressing HLA-DR as taught by the '027 patent, Selvam et al, Desormeaux et al, Saarloos et al and Catin et al. From the combined teachings

of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because not all the liposomal formulations have shown efficient drug encapsulation and drug retention and sterically stabilized liposomes have higher efficiency of drug encapsulation and drug retention by reduced leakage of entrapped drug as taught by the '027 patent (see col. 3, line 51 bridging col. 4, lines 1-27, in particular). Further, targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases as taught by the '027 patent (See col. 2, lines 25-31, col. 9, lines 7-12, in particular). HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 as taught by Catin et al (see page 1922, col. 2, in particular) that enhances the kinetics of virus infection (see abstract, in particular). Selvam et al teach tagging liposome with antibody to host-derived molecules such as CD4 acquired by HIV would allow the liposomes to be targeted to a specific cell population since HIV predominantly attacks cells that bear CD4 receptor (see page 12, col. 1, last paragraph, in particular). Saarloos et al et al teach HLA protein present at the surface of an infectious agent such as HIV is acquired from host and at the membrane surface of a cell such as CD4+ T cells and macrophage and can be detected by anti-HLA-DR antibody (see entire document, page 1641, col. 2, page 1642, col. 1, in particular). Desormeaux et al teach site-specific drug targeting may allow less frequent administrations of anti-viral agents and at low doses (reduced toxicity) than convention therapy that improves efficacy, and quality of life for patients (see page 11, Advantages and Limitations, Table 1, in particular).

Applicants' arguments filed 9/19/05 have been fully considered but are not found persuasive.

Applicants' position is that the '027 patent does not discuss a HLA-DR ligand and even less a HLA-DR ligand coupled to a lipid comprising vesicle as claimed in any one of claims 3-9 and/or containing drugs as claimed in claim 19. The '027 patent alone or in combination with Selvam and/or Cantin do not teach the formulation comprising a ligand capable of binding to a protein present at the surface of an infectious agent and at the membrane surface of a cell.

In response, Saarloos et al teach a ligand such as anti-HLA-DR that binds to HLA protein (MHC class II) present at the surface of an infectious agent such as HIV plasma and at the membrane surface of a cell such as CD4+ T cells and macrophage (see entire document, page 1641, col. 2, page 1642, col. 1, in particular). The claimed invention differs from the combined teachings of Selvam et al, Desormeaux et, Saarloos et al and Catin et al only in that the liposome comprises the specific diacylphosphatidylcholine and diacylphosphatidylglycerol such as the ones recited in any one of claims 3-9.

The '027 patent teaches a formulation for treatment of viral disease such as HIV which comprises a lipid vesicle or liposome that comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10:1 and 1:1, wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length (palmitoyl which is 16 carbon or stearoyl which is 18 carbon in length) (See claim 1 of '027 patent, col. 3, lines 58-62, in particular). The reference formulation wherein the lipid component comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine (see claim 2 of '027 patent, in particular). The reference formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine and wherein the polyethyleneglycol has a molecular weight between about 500 and 5000 Daltons (See claim 11 of '027 patent, in particular). The '027 patent also teaches a formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine (DPPC) and diacylphosphatidylglycerol (DSPG) in a molar ratio of 10:3 (See col. 3, lines 46-47, in particular) and a formulation wherein the lipid component comprises a mixture of diacylphosphatidylcholine: diacylphosphatidylglycerol: diacylphosphatidylethanol-amine-polyethyleneglycol in a molar ratio of 10 to 3 to 1.45 which is between the claimed 0.1-3 (See col. 5, lines 46-47, in particular). The reference formulation further encapsulated a drug such as AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for treating viral infection (See claims 7, 9-10 of '027 patent, in particular). The '027 patent further teaches that the reference liposome formulation can be modified by coupling of antibody molecules to enhance the targeting of the liposome to the specific cells (See col. 4, lines 11-13, in particular) that are HIV reservoirs as well as marked improvement of the pharmacokinetics of drugs (See abstract, in particular). The '027 patent teaches that targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could

reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases (See col. 2, lines 25-31, col. 9, lines 7-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the liposome that coupled to anti-HLA-DR capable of binding to a HLA-DR protein as taught by Selvam et al, Desormeaux et al, Saarloos et al and Catin et al for the specific liposome and/or containing drug such as AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for targeting said liposome containing drug to infectious agent such as HIV or cells such as CD4+ T cells or macrophage expressing HLA-DR as taught by the '027 patent, Selvam et al, Desormeaux et al, Saarloos et al and Catin et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

12. Claims 11 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selvam et al (of record, Antiviral Research 33: 11-20, 1996; PTO 1449) or Desormeaux et al (J Drug Targeting 6(1): 1-15, 1998; PTO 1449) each in view of Saarloos et al (J Virology 71(3): 1640-1643, Feb 1997; PTO 892) and Catin et al (of record, J Virology 71(3): 1922-1930, March 1997; PTO 892) as applied to claims 1-2, 10-18 and 24 and further in view of Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629).

The combined teachings of Selvam et al, Desormeaux et al, Saarloos et al and Catin et al or have been discussed supra.

The claimed invention in claims 11 and 20 differs from the teachings of the combined references only in that the formulation wherein the ligand is an antibody fragment.

Harlow *et al* teach a method of producing antibody fragment such as Fab or F(ab')₂ fragment (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment as taught by Harlow et al using the whole anti-HLA-DR as taught by Saarloos et al that is coupled to the liposome formulation as taught by Desormeaux et al, Selvam et al and Catin et al. From the combined teachings of the references,

Art Unit: 1644

it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody and antibody fragment because Harlow *et al* teach that fragments of antibodies can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular). One having ordinary skill in the art would have been motivated to do this because HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 that enhances the kinetics of virus infection as taught by Catin (see page 1922, col. 2, abstract, in particular). Selvam *et al* teach tagging liposome with antibody to host-derived molecules acquired by HIV would allow the liposomes to be targeted to a specific cell population since HIV predominantly attacks cells that bear CD4 receptor (see page 12, col. 1, last paragraph, in particular). Saarloos *et al et al* teach anti-HLA-DR antibody that binds to HLA protein present at the surface of an infectious agent such as HIV and at the membrane surface of a cell such as CD4+ T cells and macrophage (see entire document, page 1641, col. 2, page 1642, col. 1, in particular). Desormeaux *et al* teach site-specific drug targeting may allow less frequent administrations of anti-viral agents and at low doses (reduced toxicity) than convention therapy that improves efficacy, and quality of life for patients (see page 11, Advantages and Limitations, Table 1, in particular).

Applicants' arguments filed 9/19/05 have been fully considered but are not found persuasive.

Applicants' position is that the teachings of Selvam and Cantin have been discussed *supra*. Harlow reference does not discuss a HLA-DR ligand, and even less a HLA-DR ligand coupled to a lipid comprising vesicle. There is no teachings or suggestion in the Harlow *et al* reference, taken alone or in combination with Selvam and/or Cantin, of a formulation comprising a ligand capable of binding to a protein present at the surface of an infectious agent and at the membrane surface of a cell.

In response, Saarloos *et al* teach a ligand such as anti-HLA-DR (class II MHC) that binds to HLA protein present at the surface of an infectious agent such as HIV plasma and at the membrane surface of a cell such as CD4+ T cells and macrophage (see entire document, page 1641, col. 2, page 1642, col. 1, in particular). The combined teachings of Selvam *et al*, Desormeaux *et al*, Saarloos *et al* and Catin *et al* or have been discussed *supra*.

The claimed invention in claims 11 and 20 differs from the teachings of the combined references only in that the formulation wherein the ligand is an antibody fragment.

Harlow *et al* teach a method of producing antibody fragment such as Fab or F(ab')₂ fragment (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment as taught by Harlow *et al* using the whole anti-HLA-DR as taught by Saarloos *et al* that is coupled to the liposome formulation as taught by Desormeaux *et al*, Selvam *et al* and Catin *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. One having ordinary skill in the art would have been motivated to make antibody and antibody fragment because Harlow *et al* teach that fragments of antibodies can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular).

13. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0286418 A1 (December 10, 1988; PTO 1449) as evidence by Saarloos *et al* (J Virology 71(3): 1640-1643, Feb 1997; PTO 892) in view of US Pat No 5,773,027 (of record, June 30, 1998; PTO 892).

The teachings of the EP 0286418 A1 patent as evidence by Saarloos *et al* have been discussed supra. The EP 0286418 A1 patent further teaches antibodies and binding fragment thereof conjugated to liposome that are effective in selectively targeting liposomes containing drug to the cell type such as lymphocytes and virus without apparent side effects or toxicity (see page 15, lines 20-20-21, in particular).

The invention in claim 3 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10: 1 and 1:1 wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length.

The invention in claim 4 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine.

The invention in claim 5 differs from the teachings of the reference only in that the formulation wherein the liposome wherein the polyethyleneglycol has a molecular weight between 500 and 5000 daltons.

The invention in claim 6 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio is 10: 3.

The invention in claim 7 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine: diacylphosphatidylglycerol: diacylphosphatidylethanolamine polyethyleneglycol in a molar ratio of 10:3:0.1-3.

The invention in claim 8 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol in a molar ratio of 10:3 or distearoylphosphatidylcholine: distearoylphosphatidylglycerol in a molar ratio of 10:3.

The invention in claim 9 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol: dipalmitoylphosphatidylethanolamine-polyethyleneglycol in a molar ratio of 10:3:0.33 or dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol in a molar ratio of 10:3:0.83.

The invention in claim 19 differs from the teachings of the reference only in that the formulation which comprises a drug wherein the drug is selected from the group consisting of ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin.

The '027 patent teaches a formulation for treatment of viral disease such as HIV which comprises a lipid vesicle or liposome that comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10:1 and 1:1, wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length (palmitoyl which is 16 carbon or stearoyl which is 18 carbon in length) (See claim 1 of '027 patent, col. 3, lines 58-62, in particular). The reference formulation wherein the lipid component comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine (see claim 2 of '027 patent, in particular). The reference formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine and wherein the polyethyleneglycol has a molecular weight between about 500 and 5000 Daltons (See claim 11 of

'027 patent, in particular). The '027 patent also teaches a formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine (DPPC) and diacylphosphatidylglycerol (DSPG) in a molar ratio of 10:3 (See col. 3, lines 46-47, in particular) and a formulation wherein the lipid component comprises a mixture of diacylphosphatidylcholine: diacylphosphatidylglycerol: diacylphosphatidylethanol-amine-polyethyleneglycol in a molar ratio of 10 to 3 to 1.45 which is between the claimed 0.1-3 (See col. 5, lines 46-47, in particular). The reference formulation further encapsulated a drug such as AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for treating viral infection (See claims 7, 9-10 of '027 patent, in particular). The '027 patent further teaches that the reference liposome formulation can be modified by coupling of antibody molecules to enhance the targeting of the liposome to the specific cells (See col. 4, lines 11-13, in particular) that are HIV reservoirs as well as marked improvement of the pharmacokinetics of drugs (See abstract, in particular). The '027 patent teaches that targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases (See col. 2, lines 25-31, col. 9, lines 7-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the liposome that coupled to anti-HLA-DR (class II antigen) capable of binding to a HLA-DR protein as taught by EP 0286418 A1 as evidence by Saarloos et al for the specific liposome as taught by the '027 patent and further encapsulated drug such as ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for targeting said drug to HIV as taught by the '027 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because not all the liposomal formulations have shown efficient in drug encapsulation and drug retention; sterically stabilized liposomes have higher efficiency of drug encapsulation and drug retention by reduced leakage of entrapped drug as taught by the '027 patent (see col. 3, line 51 bridging col. 4, lines 1-27, in particular). Further, targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from

Art Unit: 1644

AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases as taught by the '027 patent (See col. 2, lines 25-31, col. 9, lines 7-12, in particular). The EP 0286418 A1 patent teaches antibodies and binding fragment thereof conjugated to liposome is effective in selectively targeting liposomes containing drug to the cell type such as lymphocytes and HIV virus without apparent side effects or toxicity (see page 15, lines 20-20-21, in particular).

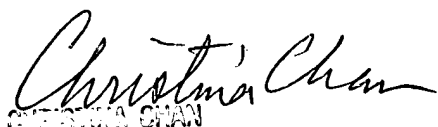
14. No claim is allowed.
15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.
16. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.

Patent Examiner

Technology Center 1600

October 28, 2005


CHRISTINA CHAN
SUBSTITUTED PATENT EXAMINER
TECHNOLOGY CENTER 1600